

Summary of Functions for Signal Transduction Transcripts Differentially Expressed in MDD

- **GRB2** (growth receptor binding protein 2). An adaptor protein that transduces signal from an activated growth factor receptor, culminating in the activation of Ras.
- **ITPKB** (inositol-1,4,5-triphosphate-3 kinase B). A member of a family of kinases involved in inositol triphosphate signal transduction.
- **PAK-1 (p21 activated kinase 1)**. A protein that is regulated by small-GTP binding proteins, like Ras, and is believed to directly act on the JNK1/MAP kinase signal transduction cascade.
- **PKC, beta1 (protein kinase C, beta 1)**. A protein kinase involved in several Ca^{++} and IP_3 dependent signal transduction cascades.
- **RalGDS (Ral guanine nucleotide dissociation stimulator)**. Stimulates dissociation of GDP from Ras and Ras-like (Ral) small G-proteins, thereby, increasing the rate of GTP-GDP exchange and facilitating activation of Ras/Ral proteins.
- **RAP1 (GTPase activating protein 1)**. Stimulates GTPase activity of small GTP-binding proteins, thereby terminating their activity and functionally inhibiting Ras/Ral proteins.
- **RGS20 (regulator of G-protein signaling 20)**. A GTPase activating protein that has specificity for the alpha γ subunit of heterotrimeric G-proteins. Facilitation of GTPase activity would terminate signal transduction and thus act as a negative regulator.

bFGF System Transcripts are Differentially Expressed in PFC in Subjects with MDD

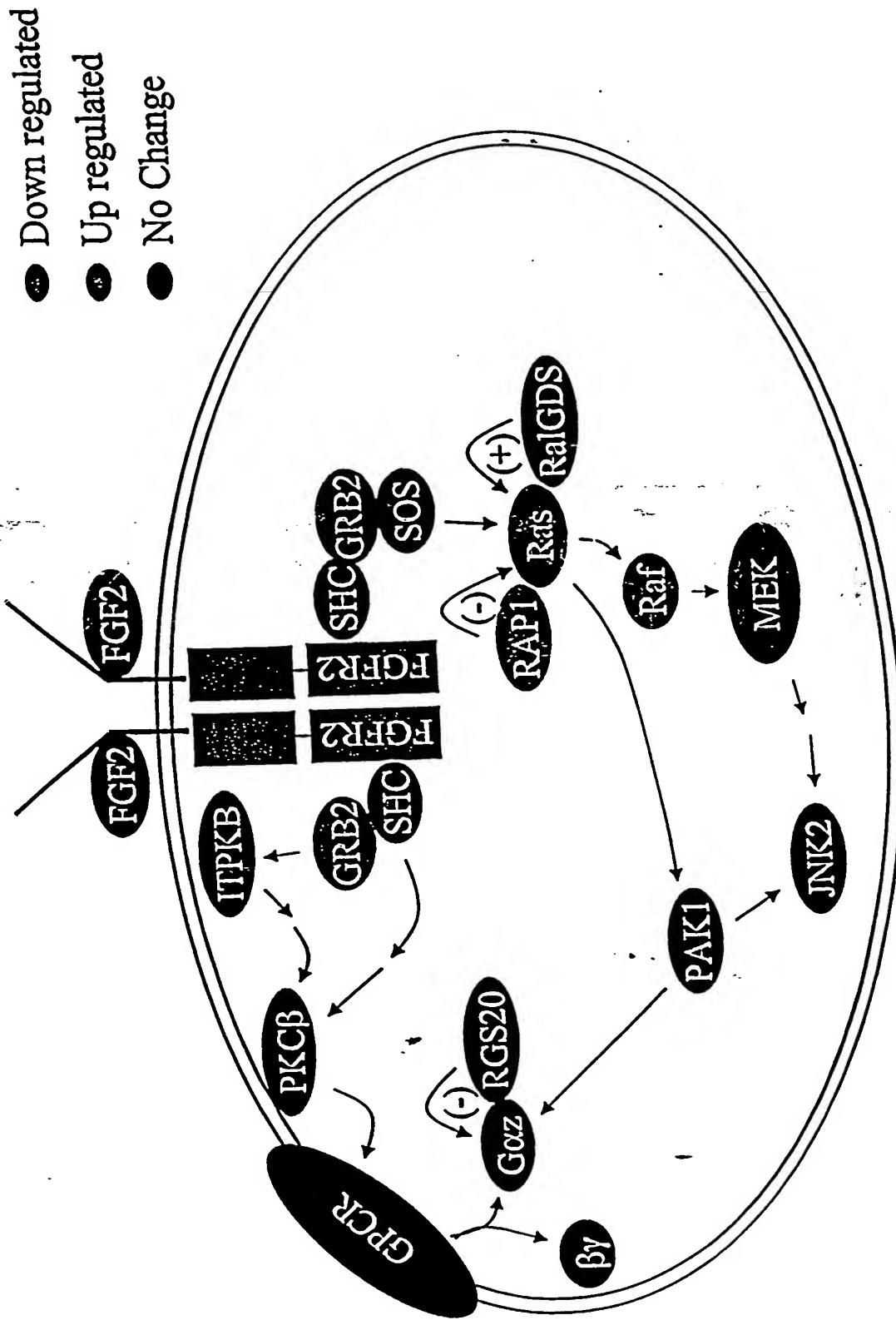


Figure 3

Fold Change and p-values for bFGF system Transcripts in PFC for MDD Subjects

probe set ID	Gene	Accession #	Fold Change	p-value
1593_at	FGF2	J04513	-1.4	0.04
1363_at	FGFR2	M877740	-1.4	0.02
1143_s_at	FGFR2	M877771	-1.2	0.04
33855_at	GRB2	M96995	-1.2	0.06
37272_at	ITPKB	X57206	-1.4	0.05
1557_at	PAK1	U24152	-1.4	0.01
1558_g_at	PAK-1	U24152	1.6	0.05
1217_g_at	PKC beta	X07409	1.6	0.02
36550_at	RalGDS	AL049538	-1.5	0.01
1270_at	RAP1	M64788	1.2	0.06
41086_at	RGS 20	AF060877	-1.6	0.04

Figure 4

Figure 5

Metabolic pathways significantly dysregulated

Pathway	GS/GOC	possibility of false positive
oxidative phosphorylation	8/95	0.00117
carotenoid biosynthesis	2/5	0.0057
vitamin E biosynthesis	3/30	0.0360
vitamin C biosynthesis	3/32	0.0425
ATP synthesis	2/17	0.0643
sterol, vitamin K/E, carotenoid biosynthesis	2/21	0.0934
Parkinson's disease	1/4	0.0955
sphingophospholipid	2/23	0.1091
nitrogen metabolism	2/24	0.1172
galactose metabolism	2/32	0.1866
glutathion metabolism	2/33	0.1957
glycine, serine, threonine metabolism		

GS/GOC; genes selected/genes on a chip

Figure 6

Signaling & Metabolic Pathways Significantly Altered in AnCg of Bipolar Subjects

- 1. Inositol Phosphate Metabolism 14/135
- 2. Nicotinate and Nicotinamide Metabolism 11/116
- 3. Benzoate Degradation N-Ac CoA Ligation 11/118
- 4. Alanine and Aspartate Metabolism 4/18
- 5. Starch and Sucrose Metabolism 11/132
- 6. Sphingoglycolipid Metabolism 11/134
- 7. Glutamate Metabolism 4/21
- 8. Phosphotyrosyl-Isositol Signaling 8/101

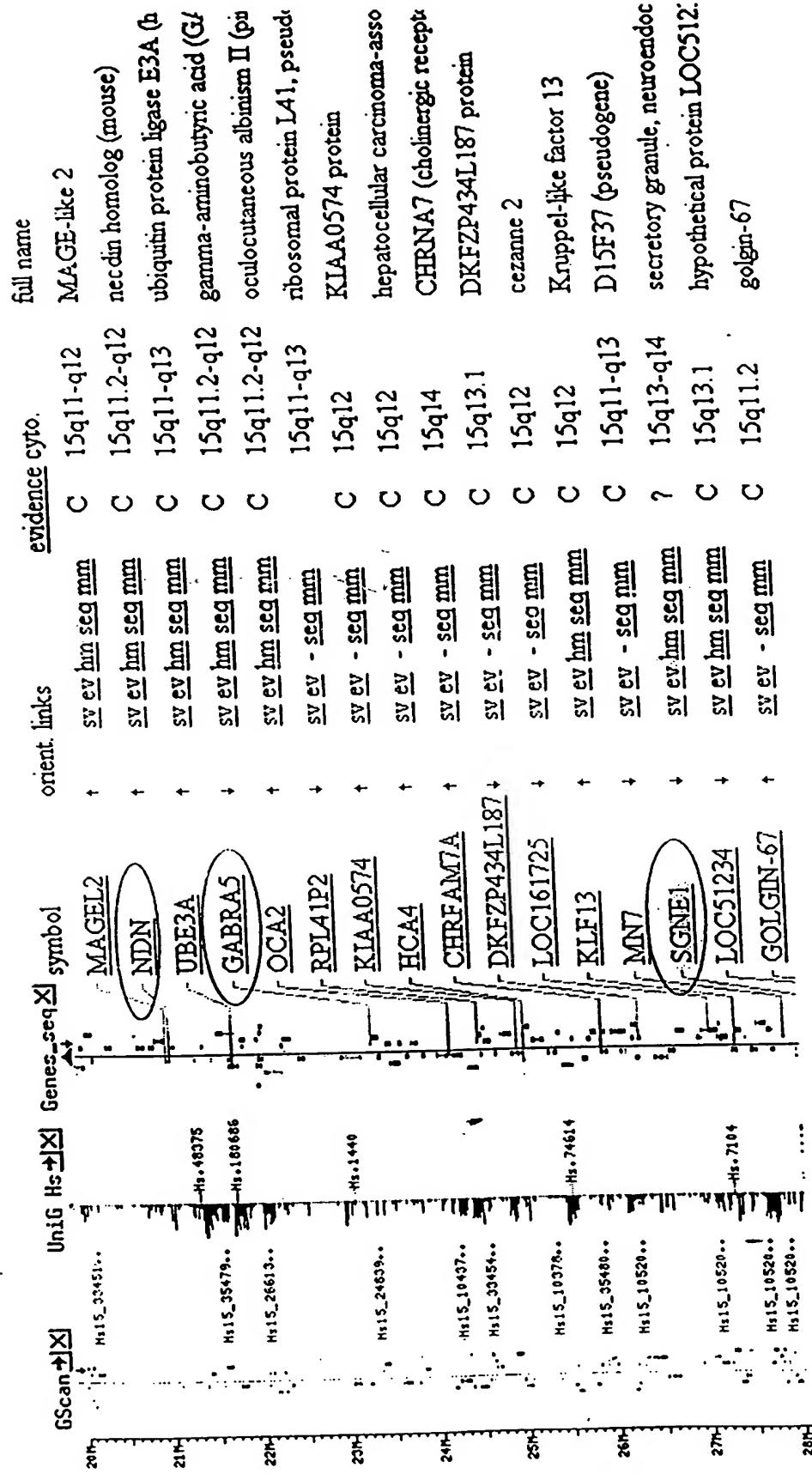
Figure 7

Three OverExpressed Genes Are Located in the Same Chromosomal Region

Symbol	Description	Cytogenetic Band (Mb)
<i>SGNE1</i>	Secretory granule, neuroendocrine protein 1 (7B2 protein)	15q13
<i>NDN</i>	Necdin homolog (mouse)	15q11.2
<i>GABRA5</i>	Gamma-aminobutyric acid (<i>GABA</i>) A receptor, alpha 5	15q11.2

Figure 8

Three of the 13 genes are on 15q11-13 within the Prader-Willi region (SGNE1, GABRA5, and NDN)

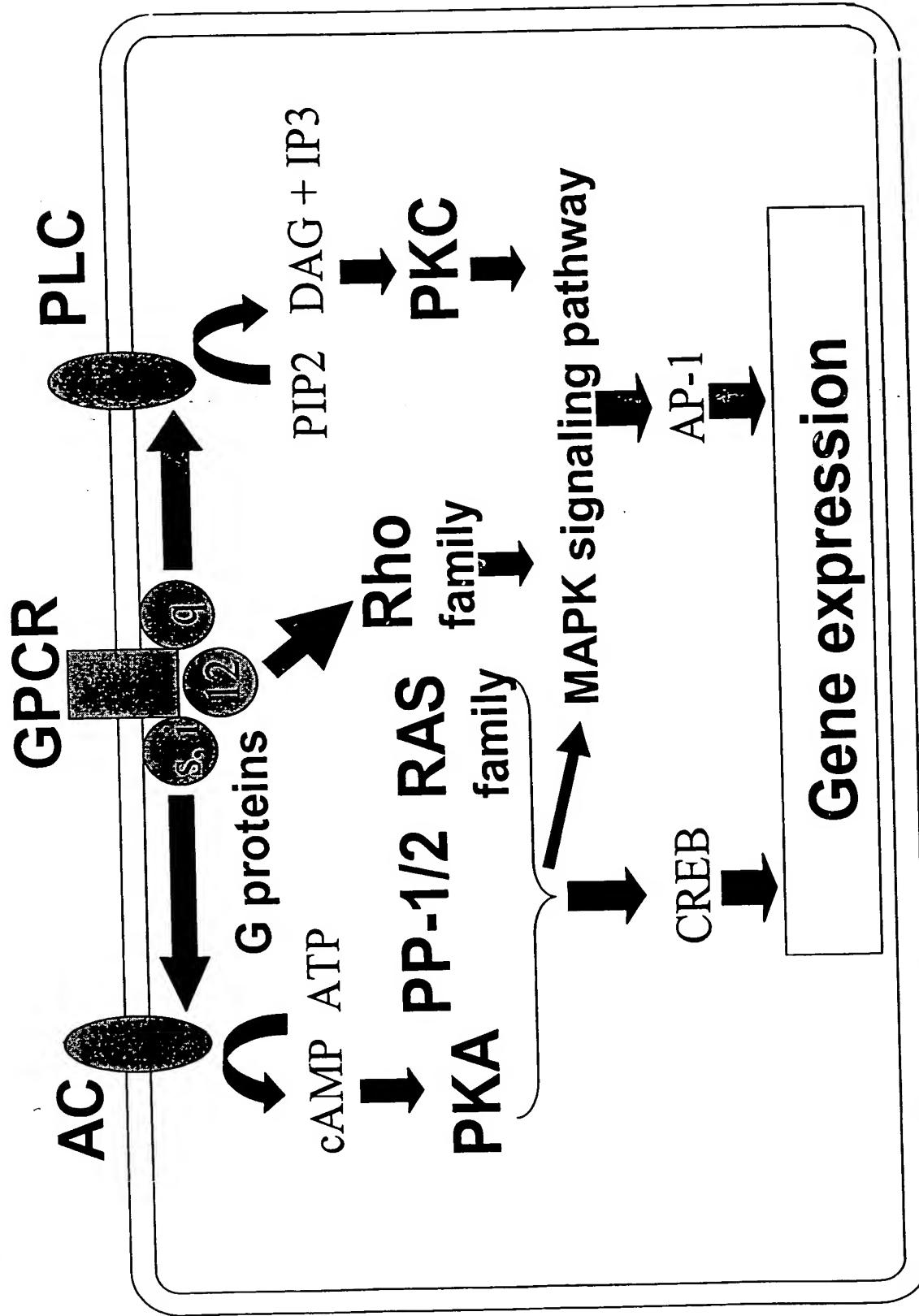


These 3 genes are found within a 7 Mb region that contains 10 other genes.

Genes Regulated in Human Postmortem Tissue (Dorsolateral PFC and Anterior Cingulate)

Figure 6

GPCR and cAMP/PI/Rho pathways

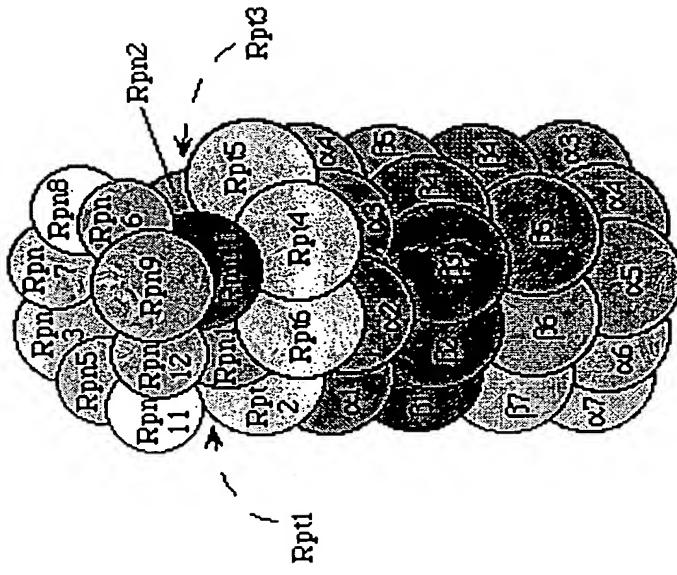


Proteasome: Alterations in In Bipolar SS, Anterior Cingulate

- 28 subunits
- Four rings of seven.
- Outer rings: alpha subunit
- Inner Rings: beta subunit
- Beta: responsible for peptidase activity.
- Degrades Short-lived and Misfolded Proteins
- Role in Ubiquitination
- ATP Dependent Activity

Note: 11 / 31 genes are significant, mostly Beta

PROTEASOME

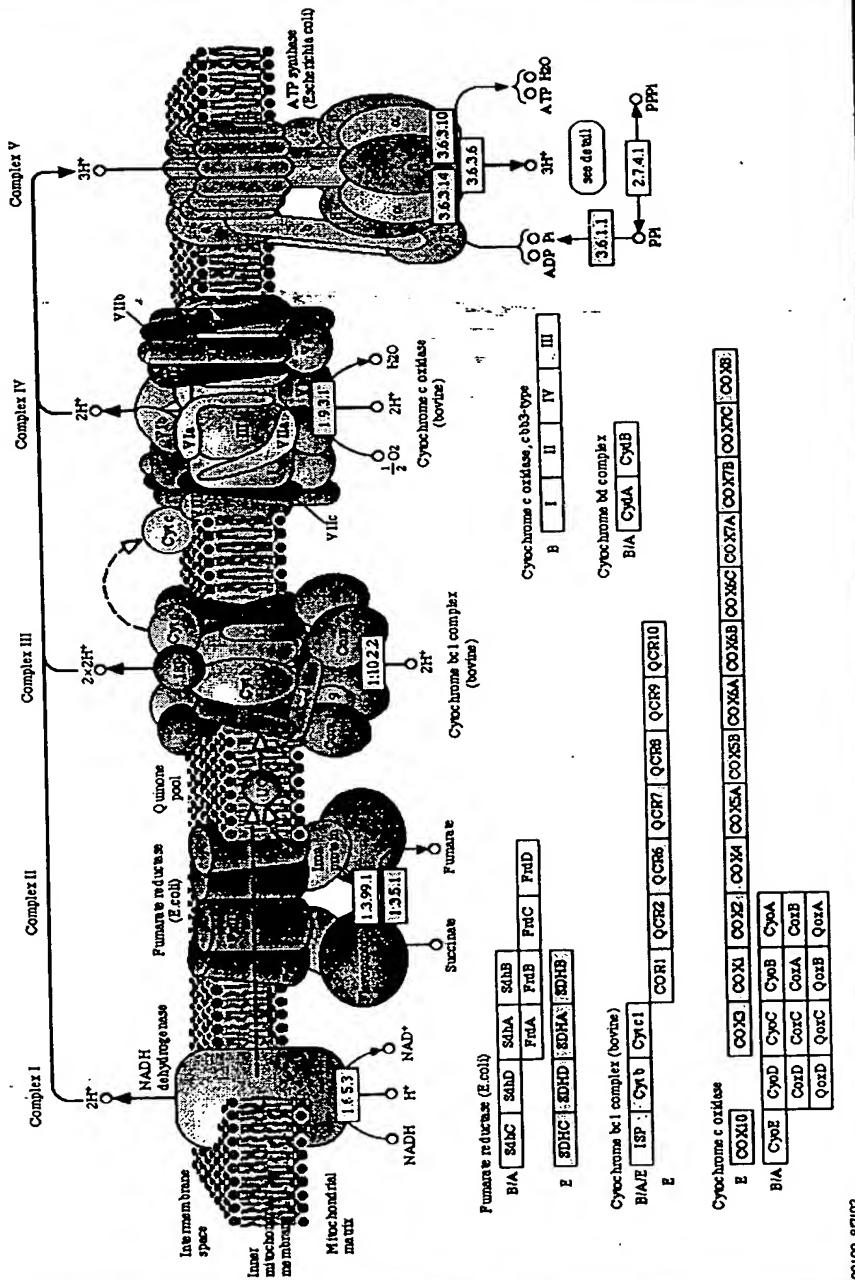


26S Proteasome (*Saccharomyces cerevisiae*)

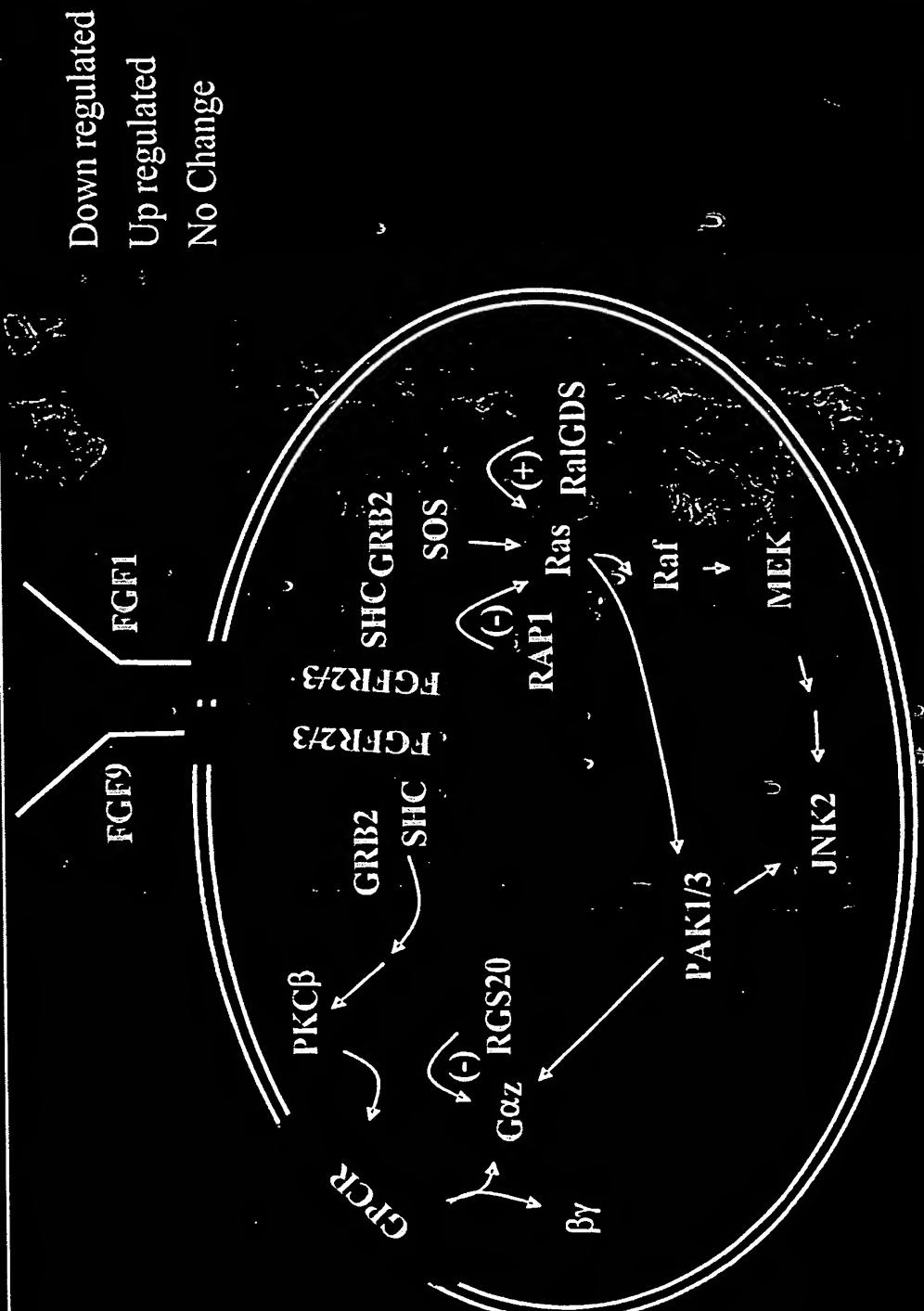
Rpn1	Rpn2	Rpn3	Rpn4	Rpn5	Rpn6
Rpn7	Rpn8	Rpn9	Rpn10	Rpn11	Rpn12
Rpt1	Rpt2	Rpt3	Rpt4	Rpt5	Rpt6
01	02	03	04	05	06
31	32	33	34	35	36

Oxidative Phosphorylation

OXIDATIVE PHOSPHORYLATION



*Major Depression, DLPEC:
FGF System Transcripts are Altered*



Real-Time PCR Confirms Microarray Results in FGF System

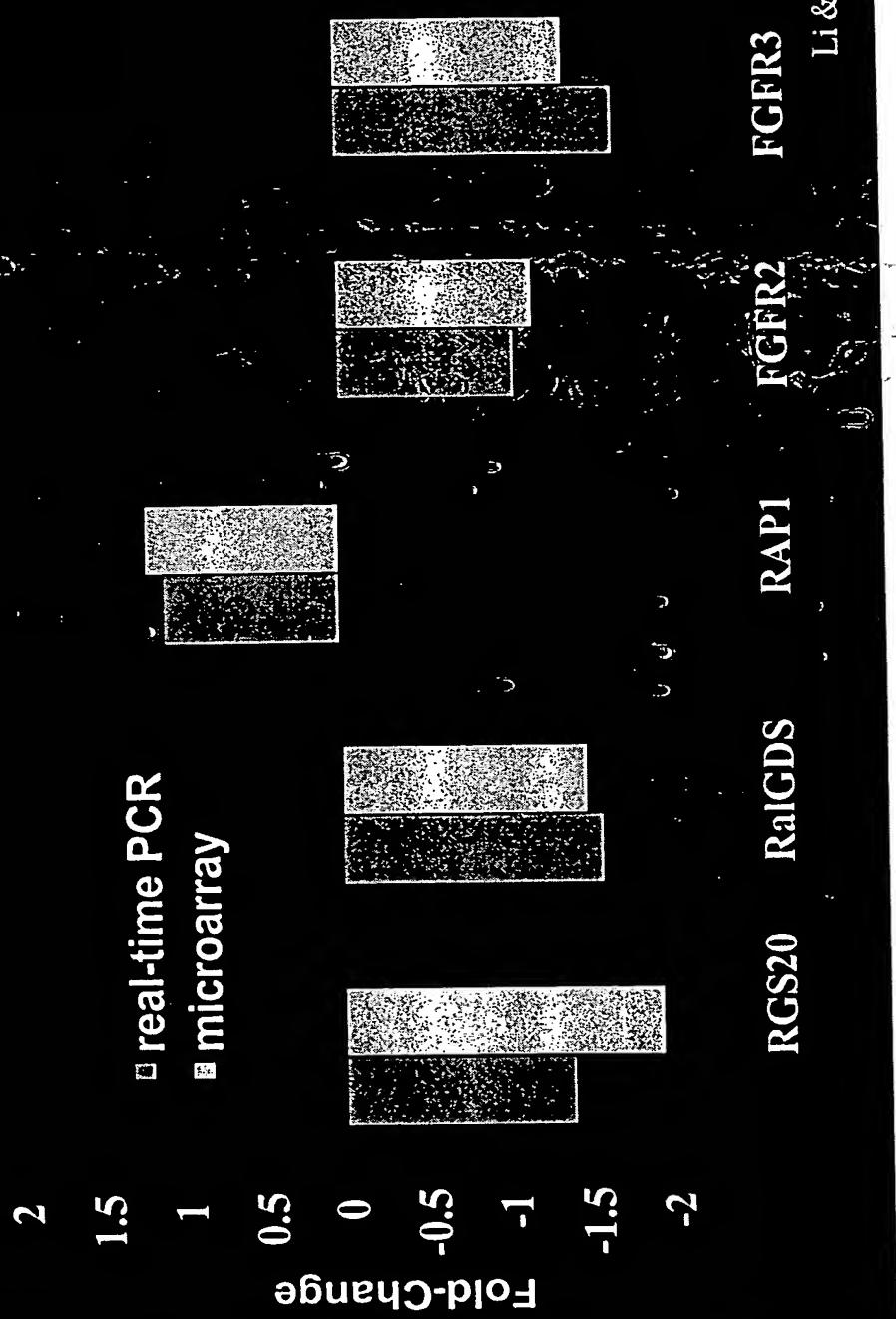


Figure 1

Li & Evans, 03

Signaling Pathways involving GABA & Glutamate

BPD_AnCg	• GABRA5	GABA A Receptor, alpha 5
	• GRIA1	Glut Receptor, ionotropic, AMPA1
	• GRM3	Glut Receptor, metabotropic 3
	• GRIA3	Glut Receptor, ionotropic, AMPA3
	• GRIK1	Glut Receptor, ionotropic, kainate1
BPD_DLPPFC	• GABRA5	GABA A Receptor, alpha 5
	• GABBR1	GABA B Receptor 1
	• GABARAPL2	GABA (A) Receptor-assoc. protein-like 2
	• (None Down)	
MDD_AnCg	• (None UP)	
	• SLC1A3	Solute carrier family 1 (glial high affinity glut transporter), member 3
	• SLC1A2	Solute carrier family 1 (glial high affinity glut transporter), member 2
	• GLUL	Glutamate-ammonia ligase (glutamine synthase)
MDD_DLPPFC	• GABARB2	GABA A receptor, beta 3
	• GABARG2	GABA A receptor, gamma 2
	• GRIA1	Glut Receptor, ionotropic, AMPA1
	• GRIK5	Glut Receptor, ionotropic, kainite 5
	• SLC1A3	Solute carrier family 1 (glial high affinity glut transporter), member 3
	• SLC1A2	Solute carrier family 1 (glial high affinity glut transporter), member 2
	• GLUL	Glutamate-ammonia ligase (glutamine synthase)

Black: Up-regulated; Red: Down-regulated